

This listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of Claims:

1-102 (Cancelled).

103. (New) A method for sterilizing a biological material that is sensitive to radiation, said method comprising:

- (i) adding to said biological material at least one flavonoid/flavonol stabilizer in an amount effective to protect said biological material from said radiation; and
- (ii) irradiating said biological material with a suitable radiation at an effective rate for a time effective to sterilize said biological material;

wherein at least one additional stabilizer is added to said biological material prior to irradiating and said at least one additional stabilizer comprises a ligand.

104. (New) The method according to claim 103, further comprising applying to said biological material at least one stabilizing process selected from the group consisting of :

- (i) reducing the residual solvent content of said biological material; and
- (ii) reducing the temperature of said biological material;

wherein said at least one stabilizing process and the amount of said flavonoid/flavonol stabilizer are together effective to protect said biological material from said radiation.

105. (New) The method according to claim 104, wherein said solvent is water.

106. (New) The method according to claim 104, wherein said residual solvent content

is reduced by the addition of an organic solvent.

107. (New) The method according to claim 104, wherein said solvent is an organic solvent.

108. (New) The method according to claim 104, wherein said biological material is suspended in an organic solvent following reduction of said residual solvent content.

109. (New) The method according to claims 103 or 104, wherein said effective rate is not more than 3.0 kGy/hour.

110. (New) The method according to claims 103 or 104, wherein said effective rate is not more than 2.0 kGy/hr.

111. (New) The method according to claims 103 or 104, wherein said effective rate is not more than 1.0 kGy/hr.

112. (New) The method according to claims 103 or 104, wherein said effective rate is not more than 0.3 kGy/hr.

113. (New) The method according to claims 103 or 104, wherein said effective rate is more than 3.0 kGy/hour.

114. (New) The method according to claims 103 or 104, wherein said effective rate is at least 6.0 kGy/hour.

115. (New) The method according to claims 103 or 104, wherein said effective rate is at least 18.0 kGy/hour.

116. (New) The method according to claims 103 or 104, wherein said effective rate is at least 30.0 kGy/hour.

117. (New) The method according to claims 103 or 104, wherein said effective rate is at least 45 kGy/hour.

118. (New) The method according to claims 103 or 104, wherein said biological material is maintained in a low oxygen atmosphere.

119. (New) The method according to claims 103 or 104, wherein said biological material is maintained in an atmosphere comprising at least one noble gas.

120. (New) The method according to claim 119, wherein said noble gas is argon.

121. (New) The method according to claims 103 or 104, wherein said biological material is maintained in a vacuum.

122. (New) The method according to claim 104, wherein said residual solvent content is reduced by a method selected from the group consisting of lyophilization, drying, concentration, addition of solute, evaporation, chemical extraction, spray-drying, and vitrification.

123. (New) The method according to claim 104, wherein said residual solvent content

is less than 15%.

124. (New) The method according to claim 104, wherein said residual solvent content is less than 3%.

125. (New) The method according to claim 104, wherein said residual solvent content is less than 2%.

126. (New) The method according to claim 104, wherein said residual solvent content is less than 1%.

127. (New) The method according to claim 104, wherein said residual solvent content is less than 0.5%.

128. (New) The method according to claim 104, wherein said residual solvent content is less than 0.08%.

129. (New) The method according to claims 103 or 104, wherein at least one sensitizer is added to said biological material prior to irradiating.

130. (New) The method according to claims 103 or 104, wherein said ligand is heparin.

131. (New) The method according to claims 103 or 104, wherein said at least one flavonoid/flavonol stabilizer is selected from the group consisting of diosmin, silymarin, epicatechin, biacalein and rutin.

132. (New) The method according to claims 103 or 104, wherein said radiation is corpuscular radiation or electromagnetic radiation, or a mixture thereof.

133. (New) The method according to claim 132, wherein said electromagnetic radiation is selected from the group consisting of radio waves, microwaves, visible and invisible light, ultraviolet light, x-ray radiation, gamma radiation and combinations thereof.

134. (New) The method according to claims 103 or 104, wherein said radiation is gamma radiation.

135. (New) The method according to claims 103 or 104, wherein said irradiating is conducted at ambient temperature.

136. (New) The method according to claims 103 or 104, wherein said irradiating is conducted at a temperature below ambient temperature.

137. (New) The method according to claims 103 or 104, wherein said irradiating is conducted below the freezing point of said biological material.

138. (New) The method according to claims 103 or 104, wherein said irradiating is conducted below the eutectic point of said biological material.

139. (New) The method according to claims 103 or 104, wherein said irradiation is conducted at a temperature above ambient temperature.

140. (New) A composition comprising at least one biological material and at least one flavonoid/flavonol stabilizer in an amount effective to preserve said biological material for its intended use following sterilization with radiation, wherein the residual solvent content is sufficiently low to preserve said biological material during sterilization by irradiation for its intended use following sterilization with radiation and further wherein said biological material is glassy or vitrified.

141. (New) The composition according to claim 140, further comprising at least one additional stabilizer selected from the group consisting of: ascorbic acid or a salt or ester thereof; glutathione; 6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid; uric acid or a salt or ester thereof; methionine; histidine; N-acetyl cysteine; lipoic acid; sodium formaldehyde sulfoxylate; gallic acid or a derivative thereof; propyl gallate; a mixture of ascorbic acid, or a salt or ester thereof, and uric acid, or a salt or ester thereof; a mixture of ascorbic acid, or a salt or ester thereof, and 6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid; a mixture of ascorbic acid, or a salt or ester thereof, uric acid, or a salt or ester thereof, and 6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid; proteins, and a mixture of uric acid, or a salt or ester thereof and 6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid, said at least one additional stabilizer is present in an amount effective to preserve said biological material for its intended use following sterilization with radiation.

142. (New) The composition of claim 140, wherein said residual solvent content is less than 15%.

143. (New) The composition of claim 140, wherein said residual solvent content is less than 10%.

144. (New) The composition of claim 140, wherein said residual solvent content is less than 5%.

145. (New) The composition of claim 140, wherein said residual solvent content is less than 2%.

146. (New) The composition of claim 140, wherein said residual solvent content is less than 1%.

147. (New) The composition of claim 140, wherein said residual solvent content is less than 0.5%.

148. (New) The composition of claim 140, wherein said residual solvent content is less than 0.08%.

149. (New) The composition of claim 140, wherein said biological material is selected from the group consisting of monoclonal immunoglobulins, polyclonal immunoglobulins, glycosidases, sulfatases, urokinase, thrombin and Factor VIII.

150. (New) The composition of claim 140, wherein the concentration of said biological material is at least 0.5%.

151. (New) The composition of claim 140, wherein the concentration of said biological material is at least 1%.

152. (New) The composition of claim 140, wherein the concentration of said

biological material is at least 5%.

153. (New) The composition of claim 140, wherein the concentration of said biological material is at least 10%.

154. (New) The composition of claim 140, wherein the concentration of said biological material is at least 15%.

155. (New) The composition of claim 140, wherein the concentration of said biological material is at least 20%.

156. (New) The composition of claim 140, wherein the concentration of said biological material is at least 25%.

157. (New) The composition of claim 140, wherein the concentration of said biological material is at least 50%.

158. (New) A method for sterilizing a biological material that is sensitive to radiation, said method comprising:

- (i) adding to said biological material at least one flavonoid/flavonol stabilizer in an amount effective to protect said biological material from said radiation; and
- (ii) irradiating said biological material with a suitable radiation at an effective rate for a time effective to sterilize said biological material;

wherein the recovery of the desired activity of the biological material after sterilization by irradiation is greater than 100% of the pre-irradiation value.

159. (New) The method according to claim 158, further comprising applying to said biological material at least one stabilizing process selected from the group consisting of :

- (i) reducing the residual solvent content of said biological material; and
- (ii) reducing the temperature of said biological material;

wherein said at least one stabilizing process and the amount of said flavonoid/flavonol stabilizer are together effective to protect said biological material from said radiation.

160. (New) The method according to claims 158 or 159, wherein said biological material is an immunoglobulin.

161. (New) The method according to claims 158 or 159, wherein said biological material is an enzyme.

162. (New) The method according to claim 160, wherein said immunoglobulin is IgG.

163. (New) The method according to claim 162, wherein said IgG is a monoclonal immunoglobulin.

164. (New) The method according to claim 161, wherein said enzyme is thrombin.

165. (New) The method according to claim 161, wherein said enzyme is Factor VIII.

166. (New) The method according to claim 161, wherein said enzyme is urokinase.

167. (New) A method for sterilizing a biological material that is sensitive to radiation,

said method comprising:

(i) adding to said biological material at least one flavonoid/flavonol stabilizer in an amount effective to protect said biological material from said radiation; and

(ii) irradiating said biological material with a suitable radiation at an effective rate for a time effective to sterilize said biological material, wherein said effective dose rate is not constant and comprises a rate between 0.1 kGy/hr to 3.0 kGy/hr for at least a portion of said period of time and a rate of at least 6.0 kGy/hr for at least another portion of said period of time.

168. (New) The method according to claim 167, further comprising applying to said biological material at least one stabilizing process selected from the group consisting of :

(i) reducing the residual solvent content of said biological material; and

(ii) reducing the temperature of said biological material;

wherein said at least one stabilizing process and the amount of said flavonoid/flavonol stabilizer are together effective to protect said biological material from said radiation.

169. (New) The method according to claims 167 or 168, wherein said effective dose rate comprises a rate between 0.25 kGy/hr to 2.0 kGy/hr for at least a portion of said period of time and a rate of at least 6.0 kGy/hr for at least another portion of said period of time.

170. (New) The method according to claims 167 or 168, wherein said effective dose rate comprises a rate between 0.5 kGy/hr to 1.5 kGy/hr for at least a portion of said period of time and a rate of at least 6.0 kGy/hr for at least another portion of said period of time.

171. (New) The method according to claims 167 or 168, wherein said effective dose rate comprises a rate between 0.5 kGy/hr to 1.0 kGy/hr for at least a portion of said period of time and a rate of at least 6.0 kGy/hr for at least another portion of said period of time.

Reply to Office Action of September 29, 2003

172. (New) The method according to claim 168, wherein said solvent is water.
173. (New) The method according to claim 168, wherein said residual water content is reduced by the addition of an organic solvent.
174. (New) The method according to claim 168, wherein said biological material is suspended in an organic solvent following reduction of said residual solvent content.
175. (New) The method according to claims 167 or 168, wherein said effective rate further comprises a rate of least 18.0 kGy/hour for at least another portion of said period of time.
176. (New) The method according to claims 167 or 168, wherein said effective rate further comprises a rate of least 30.0 kGy/hour for at least another portion of said period of time.
177. (New) The method according to claims 167 or 168, wherein said effective rate further comprises a rate of least 45 kGy/hour for at least another portion of said period of time.
178. (New) The method according to claims 167 or 168, wherein said biological material is maintained in a low oxygen atmosphere.
179. (New) The method according to claims 167 or 168, wherein said biological material is maintained in an atmosphere comprising at least one noble gas.
180. (New) The method according to claim 179, wherein said noble gas is argon.

181. (New) The method according to claims 167 or 168, wherein said biological material is maintained in a vacuum.

182. (New) The method according to claim 168, wherein said residual solvent content is reduced by a method selected from the group consisting of lyophilization, drying, concentration, addition of solute, evaporation, chemical extraction, spray-drying, and vitrification.

183. (New) The method according to claim 168, wherein said residual solvent content is less than 15%.

184. (New) The method according to claim 168, wherein said residual solvent content is less than 3%.

185. (New) The method according to claim 168, wherein said residual solvent content is less than 2%.

186. (New) The method according to claim 168, wherein said residual solvent content is less than 1%.

187. (New) The method according to claim 168, wherein said residual solvent content is less than 0.5%.

188. (New) The method according to claim 168, wherein said residual solvent content is less than 0.08%.

189. (New) The method according to claims 167 or 168, wherein at least one sensitizer is added to said biological material prior to irradiating.

190. (New) The method according to claims 167 or 168, wherein at least one additional stabilizer is added to said biological material prior to irradiating.

191. (New) The method according to claim 190, wherein said at least one additional stabilizer is an antioxidant.

192. (New) The method according to claim 190, wherein said at least one additional stabilizer is a free radical scavenger.

193. (New) The method according to claim 190, wherein said at least one additional stabilizer is a combination stabilizer.

194. (New) The method according to claim 190, wherein said at least one additional stabilizer is a ligand.

195. (New) The method according to claim 194, wherein said ligand is heparin.

196. (New) The method according to claim 190, wherein said at least one additional stabilizer reduces damage due to reactive oxygen species.

197. (New) The method according to claim 190, wherein said at least one additional stabilizer is selected from the group consisting of: ascorbic acid or a salt or ester thereof;

glutathione; 6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid; uric acid or a salt or ester thereof; methionine; histidine; N-acetyl cysteine; lipoic acid; sodium formaldehyde sulfoxylate; gallic acid or a derivative thereof; propyl gallate and mixtures of two or more thereof.

198. (New) The method according to claim 197, wherein said mixtures of two or more additional stabilizers are selected from the group consisting of: mixtures of ascorbic acid, or a salt or ester thereof, and uric acid, or a salt or ester thereof; mixtures of ascorbic acid, or a salt or ester thereof, and 6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid; mixtures of ascorbic acid, or a salt or ester thereof, uric acid, or a salt or ester thereof, and 6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid; and mixtures of uric acid, or a salt or ester thereof, lipoic acid, sodium formaldehyde sulfoxylate, gallic acid or a derivative thereof, propyl gallate and 6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid.

199. (New) The method according to claims 167 or 168, wherein said at least one flavonoid/flavonol stabilizer is selected from the group consisting of diosmin, silymarin, epicatechin, biacalein and rutin.

200. (New) The method according to claims 167 or 168, wherein said radiation is corpuscular radiation or electromagnetic radiation, or a mixture thereof.

201. (New) The method according to claim 200, wherein said electromagnetic radiation is selected from the group consisting of radio waves, microwaves, visible and invisible light, ultraviolet light, x-ray radiation, gamma radiation and combinations thereof.

202. (New) The method according to claims 167 or 168, wherein said radiation is gamma radiation.

203. (New) The method according to claims 167 or 168, wherein said radiation is a combination of one or more wavelengths of visible and ultraviolet light.

204. (New) The method according to claims 167 or 168, wherein said irradiating is conducted at ambient temperature.

205. (New) The method according to claims 167 or 168, wherein said irradiating is conducted at a temperature below ambient temperature.

206. (New) The method according to claims 167 or 168, wherein said irradiating is conducted below the freezing point of said biological material.

207. (New) The method according to claims 167 or 168, wherein said irradiating is conducted below the eutectic point of said biological material.

208. (New) The method according to claims 167 or 168, wherein said irradiating is conducted at a temperature above ambient temperature.

209. (New) The method according to claims 167 or 168, wherein the recovery of the desired activity of the biological material after sterilization by irradiation is greater than 100% of the pre-irradiation value.

210. (New) The method according to claims 167 or 168, wherein the recovery of the desired activity of the biological material after sterilization by irradiation is at least 100% of the pre-irradiation value.

211. (New) The method according to claims 167 or 168, wherein the recovery of the desired activity of the biological material after sterilization by irradiation is at least 90% of the pre-irradiation value.

212. (New) The method according to claims 167 or 168, wherein the recovery of the desired activity of the biological material after sterilization by irradiation is at least 80% of the pre-irradiation value.

213. (New) The method according to claims 167 or 168, wherein the recovery of the desired activity of the biological material after sterilization by irradiation is at least 70% of the pre-irradiation value.

214. (New) The method according to claims 167 or 168, wherein the recovery of the desired activity of the biological material after sterilization by irradiation is at least 60% of the pre-irradiation value.

215. (New) The method according to claims 167 or 168, wherein the recovery of the desired activity of the biological material after sterilization by irradiation is at least 50% of the pre-irradiation value.

216. (New) The method according to claims 167 or 168, wherein the recovery of the desired activity of the biological material after sterilization by irradiation is less than 50% of the pre-irradiation value.

217. (New) The method according to claims 167 or 168, wherein said biological

material is an immunoglobulin.

218. (New) The method according to claim 211, wherein said biological material is an enzyme.

219. (New) The method according to claim 217, wherein said immunoglobulin is IgG.

220. (New) The method according to claim 218, wherein said IgG is a monoclonal immunoglobulin.

221. (New) The method according to claim 218, wherein said enzyme is thrombin.

222. (New) The method according to claim 218, wherein said enzyme is Factor VIII.

223. (New) The method according to claim 218, wherein said enzyme is urokinase.